## REMARKS/ARGUMENTS

Claims 114-169 and 208-213 are pending.

### 1 Novelty and Non-Obviousness

An orally administratable insulin compound is a holy grail of modern medicine. Many companies have attempted this difficult task in the past, and most have simply given up. The human trials presented in the examples in the present application are the culmination of many years of work and many millions of dollars of investment on the part of the applicants' assignee, Nobex Corporation.

The references cited by the examiner relate to the administration of certain insulin conjugates to dogs. It will be appreciated that while the dog model is predictive of efficacy in humans, a substantial amount of experimental research is required in order to determine effecitve doses in humans. There are numerous reasons for these differences, for example:

- The enzyme content of the dog gut and the human gut are dramatically different, resulting in different rates of degradation of the insulin conjugate.
- Absorption across the dog gut differs radically from absorption across the human gut.
- The enzyme content of the dog bloodstream differs from the enzyme content of the human bloodstream.
- The livers of the human and dog are different sizes and absorption rates differ, dramatically affecting the pharmacokinetics of absorbed conjugates.
- Various metabolic differences between humans and dogs mean that the amount of insulin needed by a dog's differs from the amount needed by a human.

The pending claims have been amended to clarify that the patient to which the drug is administered is a human patient. None of the references cited by the Examiner teach the administration of the specific conjugates to a human patient to achieve the specific results recited by the applicants.

The applicants' have amended their claims to emphasize that the claims are limited to administration to humans and to further emphasize the various characteristics of the claimed methods specifically discovered as the result of the clinical trials reported in the examples provided in the specification. Nothing in the cited references teaches:

- Administration to a human (claim 114)
- Administering to the human orally by ingestion (claim 114)
- Administration to the human prior to or contemporaneously with a meal (claim 114)
- Administring to the human an amount of insulin drug between about 0.05 and 10 mg per kilograms of the human patient's body weight (claim 114)
- Administration in the foregoing specific amounts to provide an insulin drug concentration in portal vein blood of a human between about 10 and 1,000 U/m[1] (claims 114 and 208)
- Achieving this concentration within about 60 minutes of administration (claim 114)
- Stabilizing peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration (claim 209)
- Reduction of hepatic glucose production in the patient by at least about 25 percent (claim 210)
- Absorption of at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient within about 120 minutes of ingestion (claim 212)

None of these specific aspects of the claims are taught or suggested by the cited art. Accordingly, the Examiner is respectfully requested to withdraw the stated 30 USC § 102 and 103 rejections.

[1] In the normal physiological state, pancreatic insulin enters the portal vein and affects the liver first, where it is removed quickly by binding and degradation. This is not the case for insulin administered peripherally or by inhallation. Nothing in the art teaches the ability to achieve the desired portal vein concentrations in a human by oral administration.

The applicants note that there can be no issue of inherency, since the cited art does not teach the administration of the claimed compounds to humans in the amounts claimed. Nor does the art teach the desirability of or enable the claimed portal vein concentrations.

## 2 Meaning of Monodispersed

With reference to the Examiner's comments about use of the term "monodispersed,"[2] the applicants note that the specification teaches:[3]

> Non-polydispersed (e.g., substantially monodispersed and monodispersed) insulin polypeptide-oligomer conjugates may be synthesized by methods provided in one or more of the following references: U.S. Patent ~~Application Serial No. 09/873,797 filed June 4, 2001~~ No. 6,858,850 issued February 22, 2005, ~~by~~ to Ekwuribe et al. ~~entitled "Mixtures of Drug-Oligomer Conjugates Comprising Polyalkylene Glycol, Uses Thereof, and Methods of Making Same"~~; U.S. Patent ~~Application Serial No. 09/873,899 filed June 4, 2001~~ No. 6,828,297 issued December 7, 2004 ~~by~~ to Ekwuribe et al. ~~entitled "Mixtures of Insulin Drug-Oligomer Conjugates Comprising Polyalkylene Glycol, Uses Thereof, and Methods of Making Same"~~; U.S. Patent ~~Application Serial No. 10/036,744 filed December 21, 2001~~ No. 6,913,903 issued July 5, 2005, ~~by~~ to Soltero et al. ~~entitled "Methods of Synthesizing Insulin Polypeptide-Oligomer Conjugates, and Proinsulin Polypeptide-Oligomer Conjugates and Methods of Synthesizing Same"~~, the disclosures of which are incorporated herein by reference in their entireties. Oligomers according to embodiments of the present invention are preferably substantially monodispersed and are more preferably monodispersed.

The cited applications are incorporated in the present application by reference and are relied on for their teaching concerning the use of the terms "substantially monodispersed" and "monodispersed" and the like. For example, U.S. Patent Application Serial No. 09/873,899 (now US Patent 6,828,297) teaches:[4]

> As used herein, the term "substantially monodispersed" is used to describe a mixture of compounds wherein at least about 95 percent of the compounds in the mixture have the same molecular weight.
>
> As used herein, the term "monodispersed" is used to describe a mixture of compounds wherein about 100 percent of the compounds in the mixture have the same molecular weight.

The meaning assigned to the terms is as described in the applicants' specification as informed by the cited patents. Thus, as the applicants contended in the January 6, 2005 Amendment, Applicants' use of the

[2] See Office Action, paragraph bridging pages 2-3.
[3] Specification of the present application, as filed, at p. 34, first paragraph, as amended herein.
[4] US Patent 6,828,297, col. 6, lines 41-49.

the purification of conjugates having specific sites of conjugation (though monodispersed conjugates may also have identical structures). This use of the term is not taught or suggested by the cited references.

## 3 Change in Entity Status

Further, the U.S. Patent and Trademark Office is hereby notified that small entity status is no longer applicable for this application.

## 4 Deposit Account

A check in the amount of $450.00 is enclosed for payment of the large entity 2-month extension fee for responding to the April 7, 2005 final Office Action. Although it is believed that no further fee is due, the Commissioner is authorized to charge any deficiencies of payment associated with Communication, or to credit any overpayment, to **Deposit Account No. 13-4365**.

## 5 Conclusions

The pending claims are now in condition for allowance. In the event that any issues remain incident to formal allowance of the application, the Examiner is requested to contact the undersigned attorney at (919) 286-8104.

Respectfully submitted,

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